▼Picato (ingenol mebutate) – Suspension of the marketing authorisation due to risk of skin malignancy

Dear Healthcare Professional,

LEO Pharma in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you of the following while a European review of the benefits and risks of ingenol mebutate is carried out:

Summary

- **The marketing authorisation of Picato (ingenol mebutate) is suspended as a precautionary measure due to growing concerns on the possible risk of skin malignancy, while EMA continues to investigate.**
- **Final results from a study comparing Picato to another medicine for actinic keratosis (imiquimod) indicate a higher occurrence of skin cancer in the treatment area with Picato.**
- **Healthcare professionals should stop prescribing Picato and consider other treatment options as appropriate.**
- **Healthcare professionals should advise patients to be vigilant for any skin lesions developing and to seek medical advice promptly should any occur.**
- **<information on batch recall to be included here at national level as relevant>.**

Background on the safety concern

Picato (ingenol mebutate) is used for the treatment of actinic keratosis in adults when the outer layer of the skin affected is not thickened or raised. It is available as 150 micrograms/gram gel (for use on the face and scalp) and 500 micrograms/gram gel (for use on the trunk and extremities).

The potential for Picato to induce skin malignancy was already considered at the time of the initial marketing authorisation. Since then several studies have found a higher incidence in skin tumours in the treatment area in patients having used ingenol mebutate or a related ester, namely:

- higher incidence of squamous cell carcinoma with ingenol mebutate compared with imiquimod in the final results of a 3-year safety study in 484 patients (3.3% versus 0.4% of patients);
- higher incidence of benign tumours compared with vehicle in pooled 8-week trials with ingenol mebutate in 1262 patients (1.0% versus 0.1% of patients);
- higher incidence of tumours, including basal cell carcinoma, Bowen's disease and squamous cell carcinoma, was also seen compared with vehicle in four clinical trials with ingenol disoxate (an ester related to ingenol mebutate whose development has been stopped) in 1234 patients (7.7% versus 2.9% of patients).

Post-marketing reports of skin tumours in Picato-treated patients have also been received. Time to onset ranged from weeks to months.

While a number of uncertainties remain and EMA is still reviewing the available data, taking into account the growing concerns on the possible risk of skin malignancy, EMA has recommended as a precaution an EU-wide suspension of Picato.

Call for reporting

Please remember to report any adverse drug reaction suspected to be associated with Picato to in accordance with the national spontaneous reporting system, <details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>.

▼ Picato is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>.

Annexes *(if applicable)*

<Link/reference to other available relevant information, such as information on the website of a competent authority>.

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Picato (ingenol mebutate)
Marketing authorisation holder(s)	LEO Laboratories Ltd.
Safety concern and purpose of the communication	Suspension of the marketing authorisation due to risk of skin malignancy
DHPC recipients	General practitioners, dermatologists, pharmacists and other HCPs to be agreed at national level.
Member States where the DHPC will be distributed	All EEA countries

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	16 January 2020
Submission of translated DHPCs to the national competent authorities for review	20 January 2020
Agreement of translations by national competent authorities	22 January 2020
Dissemination of DHPC	27 January 2020